927-3 Time Release Characteristics of a Biodegradable Stent Coating with Polylactic Acid Releasing PEG-Hirudin and PGI2-Analog

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A major problem of stent implantation is the activation of coagulation leading to acute stent thrombosis. We approached this problem by coating of stents using a new polylactide acid carrier containing 5% PEG-Hirudin and 1% PGI2-analog to reduce thrombogenicity and local platelet activation. In this study we examined time release characteristics of the carrier and of the incorporated drugs. *Methods:* Twenty 7 mm long coated metallic stents were immersed in a constant flow of human plasma at 37ºC under sterile conditions. Weight, aPTT, collagen induced thrombocyte aggregation and it's maximum gradient were measured. *Results:* The carrier was found to degrade at a rate of 10% within 30 days. Time release characteristics of PEG-Hirudin were determined by aPTT-values, whereas those of the prostacycline analog were measured by collagen induced platelet thrombocyte aggregation.

Release of total content:

Time	10 min	1 h	6 h	12 h	24 h	48 h	4 days	6 days	16 days	30 days
PEG-Hirudin (%)	5.3	9.4	26.4	33.5	39.4	41.8	47.6	52.4	52.8	52.8
PGI2 (%)	0.9	2.1	3.4	3.8	4.4	5.0	7.1	9.4	11.2	11.8

While providing an effective local antithrombotic effect, the content of PGI2 (2 μg) and PEG-Hirudin (10 μg) in the coating of a 7 mm metallic stent is by a factor of 10^5 below the dosage needed for a systemic effect. Other studies with a human stase model have shown that the coating with PEG-Hirudin and Iloprost in combination has a synergistic effect with regard to anticoagulation. Investigation of markers of activated coagulation such as TAT III and F1-2 support these findings. *Conclusion:* While PEG-Hirudin has a fast initial release, PGI2 releases more gradually. Both drugs exhibit a local antithrombotic effect for at least 30 days at concentrations far below the systemic dose.

927-4 Influence of Stent Length and Heparin Coating on Platelet Activation: a Flow Cytometric Analysis

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Platelets are involved in the pathophysiology of acute and subacute thrombotic occlusions of stents in coronary arteries. In an in vitro model of stent thombosis we investigated the expression of activation dependent glycoproteins (GP) on platelets by flow cytometry. *Method:* Coronary stents (each n = 7) were placed in one of two parallel silicon tubings with circulating citrated platelet rich plasma (PRP) to measure 1.) platelet activation (PA) vs control without stent 2.) influence of stent length on PA 3.) influence of heparin coating on PA and 4.) time until stent thrombosis (TST). After recalcification aliquots of PRP were taken over 10 min in 2 min intervals. Blood samples were immediately fixed and stabilized. For flow cytometric analysis monoclonal antibodies CD41a (GPIIb/IIIa), CD42b (GPIb), CD62p (P-selectin) and CD63 (GP53) were used.

Results: Within 2 min after start of circulation, the expression of CD62p and CD63 increased in the tubing system with the stent. Over 10 min PA progressively increased. Longer stents led to more PA than shorter stents. Heparin coating had no influence on PA, but prolonged TST. Results are expressed as mean channel fluorescence intensity (MCFI).

	Control	15 mm	25 mm	Heparin coated	Uncoated
CD62p	35.8 ± 14.1	45.2 ± 12.0	56.2 ± 17.3	52.5 ± 12.7	50.3 ± 11.7
CD63	30.7 ± 7.9	39.7 ± 9.0	49.6 ± 11.5	30.2 ± 3.2	29.4 ± 3.1
TST (min)	20.0 ± 4.4	16.6 ± 3.8	12.2 ± 4.8	21.5 ± 5.3	

MCFI: 15 mm vs 25 mm $p < 0.005$; 15 mm vs control $p < 0.005$; 25 mm vs control $p < 0.0001$, heparin coated vs uncoated $p <$ n.s. TST: heparin coated vs uncoated $p < 0.001$, 15 mm vs 25 mm $p < 0.05$, 15 mm vs control $p < 0.01$, 25 mm vs control $p < 0.0001$. CD41a and CD42b did not show significant changes. *Conclusion:* In our in vitro model there is stent induced PA. This activation is dependent on stent length but independent of heparin coating. TST is dependent on stent length and prolonged with heparin coated stents. Flow cytometry could be used to quantify PA for optimizing stent design and material.

927-5 Differences in Coronary Platelet Deposition After Stenting and PTCA

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Acute thrombosis usually occurs in the first few hours after PTCA. However, with intracoronary stenting this clinical event is rare in the first 24 hours. Limited data is available to evaluate the underlying mechanisms explaining this phenomenon. Since platelet activation and aggregation is pivotal in thrombus formation after percutaneous revascularization procedures, we compared the platelet deposition after PTCA and stenting in a porcine coronary model.

Methods: Animals (n = 12) were pretreated with ASA (650 mg) and given heparin to achieve an ACT > 300 seconds. After intraarterial nitroglycerin administration, on-line QCA measurements were obtained in each coronary artery. Platelets (PLT) were labeled using Chromium-51 and reinfused into the animal. PTCA and metal stent implantations were performed aiming a balloon to artery ratio (BAR) 1.1–1.2:1. Animals were euthanized at 1 and 24 hours. The hearts were perfused in vivo and the stent and PTCA arterial segments were harvested for gamma counting.

Results are summarized below:

PLT × 10^7/cm^2	PTCA (n = 22)	Stent (n = 20)	p
1 hour	3.15 ± 3.17	1.34 ± 1.69	0.08
24 hour	0.70 ± 1.17*	4.36 ± 1.62†	0.002

Means ± SD; Mann Whitney. *p = 0.06 vs 1 h, †p = 0.001 vs 1 h

Conclusions: One hour after metallic stent implantation, PLT deposition does not appear to be increased compared to PTCA. However, at 24 hours, stents are associated with greater PLT deposition. Thus, between 1 and 24 hours a significant PLT accumulation occurs with stents but not with PTCA. This may have important clinical implications when trying to reduce PLT deposition after percutaneous revascularization procedures.

927-6 Effectiveness of Aspirin Alone Compared with a Combination of Ticlopine and Aspirin for the Prevention of Subacute Stent Thrombosis after Successful Optimized Stent Implantation

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Previous studies have shown that antiplatelet therapy alone can effectively prevent subacute stent thrombosis (SST) after optimized stent implantation. However, it is unknown whether ticlopidine combined with aspirin is superior to aspirin alone in preventing SST. From March 1993 to July 1995 801 consecutive patients (pts) assigned to receive either aspirin alone 325 mg each day (ASA, 264 pts, 348 lesions) or a combination of ticlopidine 250 mg two times a day and aspirin 325 mg a day (TIC-ASA, 537 pts, 737 lesions) after a successful stent insertion, in most accomplished with intravascular ultrasound guidance, were retrospectively evaluated. At one month follow-up between the ASA and TIC-ASA groups there was no difference in the rate of SST (1.9% vs 1.3%, $p = 0.5$) and cumulative major adverse clinical events (myocardial infarction, death, repeat intervention, emergency bypass surgery) (1.9% vs 2.0%, $p = 1$). Although these results indicate that there is no significant gain in clinical efficacy by combining ticlopidine and aspirin therapy, it is noteworty that in the patients who suffered SST in the ASA group, compared with the patients with SST in the TIC-ASA group, there was a trend for a lower number of the "classical" risk factors for stent thrombosis (2.6 ± 1.5 vs 4.0 ± 1.4 $p = 0.14$), with absence of filling defects indicative of thrombus, no TIMI flow <3, no bailout stent procedures done, and only one case of LAD stenting, suggesting that aspirin alone could be less protective than the combined antiplatelet regimen in preventing SST. *Conclusions:* At one month clinical follow-up SST and other adverse major clinical outcomes were not significantly different between the ASA and TIC-ASA groups. These results support the efficacy of aspirin alone in preventing stent thrombosis. However, until the results of a large randomized trial will be known, it seems reasonable to recommend aspirin mono-therapy to those patients that after optimal stent implantation have no more than 2 of the "classical" risk factors for stent thrombosis.

927-19 Integrated Mechanisms of Experimental Stent Thrombosis

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Background: The mechanisms of stent thrombosis (ST) are incompletely understood. We tested the hypothesis that three general factors which affect intravascular thrombosis: local surface, rheology, and systemic coagulation status, also modulate stent thrombosis. *Methods and Results: Effect of local*